

# Drug Class Review on Beta Blockers



## Update #5: Preliminary Scan Report #1

November 2010

**The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.**

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## OBJECTIVE:

The purpose of this preliminary updated literature scan process is to provide the Washington State Health Care Authority with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with the Washington State Health Care Authority's consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Washington State Health Care Authority ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, comparative effectiveness reviews and actions taken by the FDA or Health Canada on serious harms since the last report. Other important studies could exist.

## Date of Last Update:

Update #4 Final Report was completed in July 2009.

## SCOPE AND KEY QUESTIONS:

### Key Questions

1. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in effectiveness?
2. For adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices, do beta blocker drugs differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), or co-morbidities (drug-disease interactions) for which one beta blocker is more effective or associated with fewer adverse effects?

### Inclusion Criteria

#### Populations

Adult patients with hypertension, angina, coronary artery bypass graft, recent myocardial infarction, heart failure, atrial arrhythmia, migraine or bleeding esophageal varices

#### Interventions

Interventions include an oral beta blocker compared with another beta blocker, another drug (such as calcium channel blocker), or placebo. (Oral beta blockers: acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, carvedilol phosphate, labetalol, metoprolol tartrate, metoprolol succinate, nadolol, nebivolol, penbutolol, pindolol, propranolol, propranolol LA, timolol)

Effectiveness outcomes

Hypertension	<ol style="list-style-type: none"> <li>1. All-cause and cardiovascular mortality</li> <li>2. Cardiovascular events (stroke, myocardial infarction, or development of heart failure)</li> <li>3. End-stage renal disease (including dialysis or need for transplantation) or clinically significant and permanent deterioration of renal function (increase in serum creatinine or decrease in creatinine clearance)</li> <li>4. Quality-of-life</li> </ol>
Chronic stable angina (treatment duration $\geq 2$ months)	<ol style="list-style-type: none"> <li>1. Exercise tolerance</li> <li>2. Attack frequency</li> <li>3. Nitrate use</li> </ol>
Post-coronary artery bypass graft (long-term treatment)	<ol style="list-style-type: none"> <li>1. All-cause mortality</li> <li>2. Ischemic events (MI, unstable angina, need for repeat CABG and PTCA)</li> </ol>
Recent myocardial infarction (with and without LV dysfunction)	<ol style="list-style-type: none"> <li>1. All-cause and cardiovascular mortality</li> <li>2. Cardiovascular events (usually, development of heart failure)</li> </ol>
Symptomatic chronic heart failure	<ol style="list-style-type: none"> <li>1. All-cause or cardiovascular mortality</li> <li>2. Symptomatic improvement (heart failure class, functional status, visual analogue scores)</li> <li>3. Hospitalizations for heart failure</li> </ol>
Asymptomatic LV dysfunction	<ol style="list-style-type: none"> <li>1. All-cause and cardiovascular mortality</li> <li>2. Cardiovascular events (usually, development of heart failure)</li> </ol>
Atrial arrhythmia	<ol style="list-style-type: none"> <li>1. Rate control</li> <li>2. Relapse into atrial fibrillation</li> </ol>
Migraine	<ol style="list-style-type: none"> <li>1. Attack frequency</li> <li>2. Attack intensity/severity</li> <li>3. Attack duration</li> <li>4. Use of abortive treatment</li> </ol>
Bleeding esophageal varices	<ol style="list-style-type: none"> <li>1. All-cause mortality</li> <li>2. Fatal/non-fatal rebleeding</li> </ol>

Harms

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events reported
- Specific adverse events

Study designs

1. For effectiveness, randomized controlled trials and good-quality systematic reviews
2. For harms, controlled clinical trials and observational studies

## METHODS

### Literature Search

To identify relevant citations, we searched MEDLINE (January 2009 to October 2010). We used terms for included drugs and limits for humans, English and controlled clinical trials. To identify recent comparative effectiveness reviews, we searched the websites of the US Agency for Healthcare Research and Quality, AHRQ, ([www.ahrq.gov](http://www.ahrq.gov)) and the Canadian Agency for Drugs and Technologies in Health, CADTH, ([www.CADTH.ca](http://www.CADTH.ca)). We searched FDA and Health Canada websites for identification of new drugs, indications, and alerts for serious harms. All citations were imported into an electronic database (EndNote X2).

### Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

## RESULTS

### New Drugs

None

### New Indications

None

### New Safety Alerts

None

### New trials

Our MEDLINE search identified a total of 165 new citations. Of those, there are 10 new potentially relevant randomized controlled trials, including 4 head-to-head trials and 6 placebo-controlled trials (Appendix A). Characteristics of the head-to-head trials are provided in Table 1. We recognize that cardiac syndrome X, defined as angina but with normal coronary arteries, previously has not been explicitly identified as an included population. However, for this scan, we included the Sen 2009 trial that compares metoprolol and nebivolol in patients with cardiac syndrome X, for discussion of whether it would qualify as chronic stable angina.

**Table 1.Characteristics of head-to-head trials**

<b>Author Year</b>	<b>Beta Blockers</b>	<b>Population</b>
Udelson 2009	Carvedilol, carvedilol phosphate	Heart failure
Jabbour 2010	Carvedilol, metoprolol succinate, and bisoprolol	Heart failure and chronic obstructive pulmonary disease
Iliuta 2009	Betaxolol, metoprolol	coronary artery bypass grafting
Sen 2009	Metoprolol, nebivolol	Cardiac syndrome X*

\*Angina symptoms normal coronary arteries – unclear if fits within Chronic Stable Angina population

Among the publications of placebo-controlled trials, all involved patients with heart failure and 5 of 6 provide results from subanalyses of previously included trials (Table 2).

**Table 1.Characteristics of placebo-controlled trials**

<b>Author Year</b>	<b>Beta Blockers</b>	<b>Focus</b>
<b><i>New Trials</i></b>		
Hawkins 2009	Bisoprolol	Heart failure and moderate to severe chronic obstructive pulmonary disease
<b><i>Subanalyses from SENIORS trial</i></b>		
Cohen-Solal 2009	Nebivolol	Elderly heart failure patients with renal dysfunction
de Boer 2010	Nebivolol	Elderly heart failure patients with diabetes
van Veldhuisen 2009	Nebivolol	Elderly heart failure patients with impaired and preserved left ventricular ejection fraction
<b><i>Subanalyses from other previous trials</i></b>		
Castagno 2010	Bisoprolol	Patients with heart failure and renal impairment (CIBIS-II)
Ghali 2009	Metoprolol CR	Patients with heart failure and decreased renal function (MERIT-HF)

### **New comparative effectiveness reviews**

None

## APPENDIX A

### Head-to-head trials

Iliuta, L., R. Christodorescu, et al. (2009). "Prevention of perioperative atrial fibrillation with betablockers in coronary surgery: betaxolol versus metoprolol." Interactive Cardiovascular & Thoracic Surgery **9**(1): 89-93.

In this study, we tried to compare the efficacy and safety of betaxolol vs. metoprolol immediately postoperatively in coronary artery bypass grafting (CABG) patients and to determine whether prophylaxis for atrial fibrillation (AF) with betaxolol could reduce hospitalization and economic costs after cardiac surgery. Our trial was open-label, randomized, multicentric enrolling 1352 coronary surgery patients randomized to receive betaxolol or metoprolol. The primary endpoints were the composites of 30-day mortality, in-hospital AF (safety endpoints), duration of hospitalization and immobilization, quality of life, and the above endpoint plus in-hospital embolic event, bradycardia, gastrointestinal symptoms, sleep disturbances, cold extremities (efficacy plus safety endpoint). At the end of the study the incidence and probability of early postoperative AF with betaxolol was lower than with metoprolol in coronary surgery ( $P < 0.0001$ ). In the two study groups minor side effects were similar and no major complication was reported ( $P < 0.001$ ). Patient compliance was good and the general condition improved due to shortened hospitalization and immobilization with subsequent improvement in the psychological status, less arrhythmias and lack of significant side effects. In conclusion, because of its efficacy and safety, betaxolol was superior to metoprolol for the prevention of the early postoperative AF in coronary surgery.

Jabbour, A., P. S. Macdonald, et al. (2010). "Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial." Journal of the American College of Cardiology **55**(17): 1780-7.

**OBJECTIVES:** The purpose of this study was to determine the respiratory, hemodynamic, and clinical effects of switching between beta1-selective and nonselective beta-blockers in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD). **BACKGROUND:** Carvedilol, metoprolol succinate, and bisoprolol are established beta-blockers for treating CHF. Whether differences in beta-receptor specificities affect lung or vascular function in CHF patients, particularly those with coexistent COPD, remains incompletely characterized. **METHODS:** A randomized, open label, triple-crossover trial involving 51 subjects receiving optimal therapy for CHF was conducted in 2 Australian teaching hospitals. Subjects received each beta-blocker, dose-matched, for 6 weeks before resuming their original beta-blocker.

Echocardiography, N-terminal pro-hormone brain natriuretic peptide, central augmented pressure from pulse waveform analysis, respiratory function testing, 6-min walk distance, and New York Heart Association (NYHA) functional class were assessed at each visit.

**RESULTS:** Of 51 subjects with a mean age of  $66 \pm 12$  years, NYHA functional class I ( $n = 6$ ), II ( $n = 29$ ), or III ( $n = 16$ ), and left ventricular ejection fraction mean of  $37 \pm 10\%$ , 35 had coexistent COPD. N-terminal pro-hormone brain natriuretic peptide was significantly lower with carvedilol than with metoprolol or bisoprolol (mean: carvedilol 1,001 [95% confidence interval (CI): 633 to 1,367] ng/l; metoprolol 1,371 [95% CI: 778 to 1,964] ng/l; bisoprolol 1,349 [95% CI: 782 to 1,916] ng/l;  $p < 0.01$ ), and returned to

baseline level on resumption of the initial beta-blocker. Central augmented pressure, a measure of pulsatile afterload, was lowest with carvedilol (carvedilol 9.9 [95% CI: 7.7 to 12.2] mm Hg; metoprolol 11.5 [95% CI: 9.3 to 13.8] mm Hg; bisoprolol 12.2 [95% CI: 9.6 to 14.7] mm Hg;  $p < 0.05$ ). In subjects with COPD, forced expiratory volume in 1 s was lowest with carvedilol and highest with bisoprolol (carvedilol 1.85 [95% CI: 1.67 to 2.03] l/s; metoprolol 1.94 [95% CI: 1.73 to 2.14] l/s; bisoprolol 2.0 [95% CI: 1.79 to 2.22] l/s;  $p < 0.001$ ). The NYHA functional class, 6-min walk distance, and left ventricular ejection fraction did not change. The beta-blocker switches were well tolerated. **CONCLUSIONS:** Switching between beta1-selective beta-blockers and the nonselective beta-blocker carvedilol is well tolerated but results in demonstrable changes in airway function, most marked in patients with COPD. Switching from beta1-selective beta-blockers to carvedilol causes short-term reduction of central augmented pressure and N-terminal pro-hormone brain natriuretic peptide. (Comparison of Nonselective and Beta1-Selective Beta-Blockers on Respiratory and Arterial Function and Cardiac Chamber Dynamics in Patients With Chronic Stable Congestive Cardiac Failure; Australian New Zealand Clinical Trials Registry, ACTRN12605000504617). Copyright (c) 2010 American College of Cardiology Foundation. Published by Elsevier Inc. All rights reserved.

Sen, N., Y. Tavit, et al. (2009). "Nebivolol therapy improves endothelial function and increases exercise tolerance in patients with cardiac syndrome X." *Anadolu Kardiyoloji Dergisi* 9(5): 371-9.

**OBJECTIVE:** We sought to determine whether nebivolol affects coronary endothelial function and exercise induced ischemia in patients with cardiac syndrome X (CSX). **METHODS:** The study protocol undertaken was based on a single-blind randomized controlled prospective study. After a 2-week washout period, 38 patients with cardiac syndrome X were randomized to receive either nebivolol 5 mg daily ( $n=19$ ) or metoprolol 50 mg daily ( $n=19$ ) in a single-blind design for 12 weeks. The control group under study was consisted of 16 age- and gender-matched subjects with negative treadmill exercise tests. Plasma endothelial nitric oxide (NOx), L-arginine, and asymmetric dimethylarginine (ADMA) were measured in all patients at baseline and after 12 weeks of treatment. Statistical differences among groups were tested by one-way analysis of variance and unpaired samples t test for parametric; Kruskal-Wallis and Mann-Whitney U tests for non-parametric variables, respectively. A paired samples t test was used to compare continuous variables before and after drug therapy. **RESULTS:** At baseline, plasma level of NOx, L-arginine, and L-arginine/ADMA ratio were lower ( $p<0.001$  for all) in patients with CSX than in the control patients. Whereas, the plasma ADMA levels were increased in the patient group ( $p<0.001$ ). After 12 weeks of drug therapy, the patients taking nebivolol had increased levels of plasma NOx, plasma L-arginine, the L-arginine/ADMA ratio and decreased levels of plasma ADMA compared to those of the patients taking metoprolol ( $p<0.001$ ). In addition, exercise duration to 1-mm ST depression and total exercise duration significantly increased after treatment in the nebivolol group compared to the metoprolol group ( $p<0.01$ ). In the nebivolol group, Canadian Cardiovascular Society (CCS) angina classification improved by one or more categories in 12 (70%) patients, whereas it deteriorated or remained in the same category in 5 (30%) patients. Meanwhile, in the metoprolol group, the CCS angina classification improved by one or more categories in 7 (41%), whereas it deteriorated or remained in

the same category in 10 (59%) patients. **CONCLUSION:** Circulating endothelial function parameters (plasma ADMA, L-arginine, NOx levels) were impaired in patients with CSX. Nebivolol treatment was associated with better improvements in both circulating endothelial function and exercise stress test parameters than metoprolol. We believe that further studies are needed to evaluate the effects of nebivolol treatment on long-term clinical outcomes in patients with CSX.

Udelson, J. E., S. J. Pressler, et al. (2009). "Adherence with once daily versus twice daily carvedilol in patients with heart failure: the Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial." *Journal of Cardiac Failure* **15**(5): 385-93.

**BACKGROUND:** Suboptimal compliance in taking guideline-based pharmacotherapy in patients with chronic heart failure (HF) potentially increases the burden of hospitalizations and diminishes quality of life. By simplifying the medical regimen, once-daily dosing can potentially improve compliance. The Compliance And Quality of Life Study Comparing Once-Daily Controlled-Release Carvedilol CR and Twice-Daily Immediate-Release Carvedilol IR in Patients with Heart Failure (CASPER) Trial was designed to measure differential compliance, satisfaction, and quality of life in chronic HF patients taking carvedilol immediate release (IR) twice daily versus the bioequivalent carvedilol controlled-release (CR) once daily. **METHODS AND RESULTS:** CASPER was a prospective multicenter, 3-arm, parallel-group, randomized clinical trial for a 5-month period. The primary objective of the study was to evaluate and compare compliance with carvedilol IR twice daily (BID) and carvedilol phosphate CR once daily (QD) in patients with chronic HF who were taking carvedilol IR. Secondary objectives included comparisons of quality of life (Kansas City Cardiomyopathy Questionnaire), satisfaction with medication, and brain natriuretic peptide levels between subjects taking the two formulations. A total of 405 patients with chronic HF and left ventricular dysfunction were randomized to: (A) carvedilol IR twice daily, given double blind; (B) carvedilol CR taken in the morning and placebo in the afternoon, given double blind; or (C) carvedilol CR once daily, open label. Compliance was measured using the medication event monitoring system that captures time of bottle opening. The primary end point was a comparison of taking compliance (doses taken divided by total number of prescribed doses over the actual duration of the study) between the double-blind carvedilol IR BID versus the open-label carvedilol CR QD groups. Sample size estimates were based on assumptions of 75% compliance with BID dosing and 90% compliance with QD dosing. Mean compliance with carvedilol IR BID was 89.3% compared with 88.2% for carvedilol CR QD, and differential mean compliance was 1.1% (95% CI -4.4%, 6.6%; ie, not significant). There were no statistically significant differences in compliance between any of the 3 groups, nor differences in quality of life, treatment satisfaction, or physiologic measures among the 3 study arms. There were also no significant differences in adverse events or side effects among patients switching from carvedilol IR to carvedilol CR in arms B or C over the 5-month study duration compared with patients remaining on carvedilol IR. **CONCLUSIONS:** Compliance among chronic HF patients in the CASPER trial was high at baseline and unaffected by QD versus BID dosing. Over the 5-month follow-up period, there were no differences in adverse events among patients switching from carvedilol IR to CR.

## Placebo-controlled trials

Castagno, D., P. S. Jhund, et al. (2010). "Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial." European Journal of Heart Failure **12**(6): 607-16.

**AIMS:** Information on the effectiveness of beta-blockade in patients with heart failure (HF) and concomitant renal impairment is scarce and beta-blockers are underutilized in these patients. **METHODS AND RESULTS:** The Cockcroft-Gault formula normalized for body surface-area was used to estimate renal function (eGFR(BSA)) in 2622 patients with HF, left ventricular ejection fraction  $\leq 35\%$ , New York Heart Association class III/IV and serum creatinine  $< 300$  micromol/L (3.4 mg/dL) in the second Cardiac Insufficiency Bisoprolol Study II. Patients were divided into four sub-groups according to baseline eGFR(BSA) ( $< 45$ , 45-60, 60-75 and  $\geq 75$  mL/min per 1.73 m<sup>2</sup>). Cox proportional-hazards models adjusted for pre-specified confounders were used to assess the effect of bisoprolol and potential heterogeneity of effect across the eGFR(BSA) sub-groups. Older age, female-sex, diabetes and ischaemic-aetiology were more common in those with reduced eGFR(BSA). The hazard associated with bisoprolol use for all-cause mortality, the composite of all-cause mortality or HF-hospitalization and HF-hospitalization alone was consistently  $< 1.0$  across eGFR(BSA) categories with no treatment by renal-function interaction ( $P = 0.81$ ,  $P = 0.66$ ,  $P = 0.71$ , respectively). The rate of bisoprolol discontinuation was higher in patients with eGFR(BSA)  $< 45$  mL/min per 1.73 m<sup>2</sup>. Nevertheless the absolute benefit of bisoprolol was greater for patients with chronic kidney disease compared with those without. **CONCLUSION:** The beneficial effects of bisoprolol on mortality and hospitalization for worsening heart-failure were not modified by baseline eGFR(BSA). Renal impairment should not prevent the use of bisoprolol in patients with HF.

Cohen-Solal, A., D. Kotecha, et al. (2009). "Efficacy and safety of nebivolol in elderly heart failure patients with impaired renal function: insights from the SENIORS trial." European Journal of Heart Failure **11**(9): 872-80.

**AIM:** To determine the safety and efficacy of nebivolol in elderly heart failure (HF) patients with renal dysfunction. **METHODS AND RESULTS:** SENIORS recruited patients aged 70 years or older with symptomatic HF, irrespective of ejection fraction, and randomized them to nebivolol or placebo. Patients ( $n = 2112$ ) were divided by tertile of estimated glomerular filtration rate (eGFR). Mean age of patients was 76.1 years, 35% of patients had an ejection fraction of  $> 35\%$ , and 37% were women resulting in a unique cohort, far more representative of clinical practice than previous trials. eGFR was strongly associated with outcomes and nebivolol was similarly efficacious across eGFR tertiles. The primary outcome rate (all-cause mortality or cardiovascular hospital admission) and adjusted hazard ratio for nebivolol use in those with low eGFR was 40% and 0.84 (95% CI 0.67-1.07), 31% and 0.79 (0.60-1.04) in the middle tertile, and 29% and 0.86 (0.65-1.14) in the highest eGFR tertile. There was no interaction noted between renal function and the treatment effect ( $P = 0.442$ ). Nebivolol use in patients with moderate renal impairment (eGFR  $< 60$ ) was not associated with major safety concerns, apart from higher rates of drug-discontinuation due to bradycardia. **CONCLUSION:** Nebivolol is safe and has a similar effect in elderly HF patients with mild or moderate renal impairment.

de Boer, R. A., W. Doehner, et al. (2010). "Influence of diabetes mellitus and hyperglycemia on prognosis in patients  $\geq 70$  years old with heart failure and effects of nebivolol (data from the Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS])." *American Journal of Cardiology* **106**(1): 78-86.e1.

The beneficial effects of beta blockers in younger patients with heart failure (HF) due to systolic dysfunction are well established. However, data from patients  $\geq 70$  years old with diabetes mellitus and HF are lacking. The Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with heart failure [SENIORS] tested the efficacy of the vasodilator beta blocker nebivolol in patients  $\geq 70$  years old with HF and impaired or preserved left ventricular ejection fraction. In the present analysis, we evaluated the association between diabetes mellitus and baseline glucose levels on the primary outcome (all-cause mortality and cardiovascular hospitalization) and secondary end points, including all-cause mortality, cardiovascular hospitalizations, and cardiovascular mortality. Of 2,128 patients, 555 (26.1%) had diabetes mellitus. Of the 555 patients with diabetes mellitus, 223 (40.2%) experienced the primary end point compared to 484 (30.8%) of the 1,573 nondiabetic patients ( $p < 0.001$ ). For the nondiabetic patients, the rate of the primary outcome for placebo compared to nebivolol was 33.7% for the placebo group and 27.8% for the nebivolol group (hazard ratio 0.78, 95% confidence interval 0.65 to 0.93;  $p = 0.006$ ). In the diabetic subset, the rate was 40.3% for the placebo group and 40.1% for the nebivolol group (hazard ratio 1.04, 95% confidence interval 0.80 to 1.35,  $p = 0.773$ ). The subgroup interaction  $p$  value was 0.073. The baseline glucose levels in the nondiabetic patients did not significantly affect the outcomes. The effect of diabetes mellitus on outcome was independent of the left ventricular ejection fraction and was most pronounced in those with HF due to a nonischemic etiology. In conclusion, in patients  $\geq 70$  years old with HF, diabetes mellitus was associated with a worse prognosis. Nebivolol was less effective in the patients with diabetes and HF than in those with HF but without diabetes who were  $\geq 70$  years old. Copyright (c) 2010 Elsevier Inc. All rights reserved.

Ghali, J. K., J. Wikstrand, et al. (2009). "The influence of renal function on clinical outcome and response to beta-blockade in systolic heart failure: insights from Metoprolol CR/XL Randomized Intervention Trial in Chronic HF (MERIT-HF)." *Journal of Cardiac Failure* **15**(4): 310-8.

**BACKGROUND:** Limited information is available on the risk and impact of renal dysfunction on the response to beta-blockade and mode of death in systolic heart failure (HF). **METHODS AND RESULTS:** Renal function was estimated with glomerular filtration rate (eGFR) using the simplified Modification of Diet in Renal Disease (MDRD) equation. Patients from the Metoprolol CR/XL Controlled Randomized Intervention Trial in Chronic HF (MERIT-HF) were divided into 3 renal function subgroups (MDRD formula): eGFR(MDRD)  $> 60$  ( $n = 2496$ ), eGFR(MDRD) 45 to 60 ( $n = 976$ ), and eGFR(MDRD)  $< 45$  mL/min per 1.73 m<sup>2</sup> body surface area ( $n = 493$ ). Hazard ratio (HR) was estimated with Cox proportional hazards models adjusted for prespecified risk factors. Placebo patients with eGFR  $< 45$  had significantly higher risk than those with eGFR  $> 60$ : HR for all-cause mortality, 1.90 (95% confidence interval [CI], 1.28 to 2.81) comparing placebo patients with eGFR  $< 45$  and eGFR  $> 60$ , and for the combined end point of all-cause mortality/hospitalization for worsening HF (time to first event): HR, 1.91 (95% CI, 1.44 to 2.53). No significant increase in risk with

deceased renal function was observed for those randomized to metoprolol controlled release (CR)/extended release (XL) due to a highly significant decrease in risk on metoprolol CR/XL in those with eGFR < 45. For total mortality, metoprolol CR/XL vs placebo: HR, 0.41 (95% CI, 0.25 to 0.68;  $P < .001$ ) in those with eGFR < 45 compared with HR, 0.71 (95% CI, 0.54 to 0.95;  $P < .021$ ) for those with eGFR > 60; corresponding data for the combined end point was HR, 0.44 (95% CI, 0.31 to 0.63;  $P < .0001$ ) and HR, 0.75 (0.62 to 0.92;  $P = .005$ , respectively;  $P = .095$  for interaction by treatment for total mortality;  $P = .011$  for combined end point). Metoprolol CR/XL was well tolerated in all 3 renal function subgroups. CONCLUSIONS: Renal function as estimated by eGFR was a powerful predictor of death and hospitalizations from worsening HF. Metoprolol CR/XL was at least as effective in reducing death and hospitalizations for worsening HF in patients with eGFR < 45 as in those with eGFR > 60.

Hawkins, N. M., M. R. MacDonald, et al. (2009). "Bisoprolol in patients with heart failure and moderate to severe chronic obstructive pulmonary disease: a randomized controlled trial." European Journal of Heart Failure **11**(7): 684-90.

AIMS: Heart failure (HF) and chronic obstructive pulmonary disease (COPD) frequently coexist. No study has prospectively examined the effects of beta-blockade in those with both conditions. METHODS AND RESULTS: We randomized 27 patients with HF and coexistent moderate or severe COPD to receive bisoprolol or placebo, titrated to maximum tolerated dose over 4 months. The primary outcome was forced expiratory volume in 1 s (FEV(1)). The study is registered with ClinicalTrials.gov, number: NCT00702156. Patients were elderly and predominantly male. Cardiovascular comorbidity, smoking history, and pulmonary function were similar in each group (mean FEV(1) 1.37 vs. 1.26 L,  $P = 0.52$ ). A reduction in FEV(1) occurred after 4 months following treatment with bisoprolol compared with placebo (-70 vs. +120 mL,  $P = 0.01$ ). Reversibility following inhaled beta(2)-agonist and static lung volumes were not impaired by bisoprolol. All measures of health status exhibited a consistent non-significant improvement, including the Short Form 36 physical and mental component scores (2.6 vs. 0.5 and 0.8 vs. -0.3, respectively), Minnesota Living with Heart Failure Questionnaire (-2.5 vs. 3.5) and Chronic Respiratory Questionnaire (0.07 vs. -0.24). The mean number of COPD exacerbations was similar in the bisoprolol and placebo groups (0.50 and 0.31, respectively,  $P = 0.44$ ). CONCLUSION: Initiation of bisoprolol in patients with HF and concomitant moderate or severe COPD resulted in a reduction in FEV(1). However, symptoms and quality of life were not impaired.

van Veldhuisen, D. J., A. Cohen-Solal, et al. (2009). "Beta-blockade with nebivolol in elderly heart failure patients with impaired and preserved left ventricular ejection fraction: Data From SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure)." Journal of the American College of Cardiology **53**(23): 2150-8.

OBJECTIVES: In this pre-specified subanalysis of the SENIORS (Study of Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors With Heart Failure) trial, which examined the effects of nebivolol in elderly heart failure (HF) patients, we explored the effects of left ventricular ejection fraction (EF) on outcomes, including the subgroups impaired EF (< or =35%) and preserved EF (>35%).

BACKGROUND: Beta-blockers are established drugs in patients with HF and impaired EF, but their value in preserved EF is unclear. METHODS: We studied 2,111 patients;

1,359 (64%) had impaired ( $\leq 35\%$ ) EF (mean 28.7%) and 752 (36%) had preserved ( $>35\%$ ) EF (mean 49.2%). The effect of nebivolol was investigated in these 2 groups, and it was compared to explore the interaction of EF with outcome. Follow-up was 21 months; the primary end point was all-cause mortality or cardiovascular hospitalizations. RESULTS: Patients with preserved EF were more often women (49.9% vs. 29.8%) and had less advanced HF, more hypertension, and fewer prior myocardial infarctions (all  $p < 0.001$ ). During follow-up, the primary end point occurred in 465 patients (34.2%) with impaired EF and in 235 patients (31.2%) with preserved EF. The effect of nebivolol on the primary end point (hazard ratio [HR] of nebivolol vs. placebo) was 0.86 (95% confidence interval: 0.72 to 1.04) in patients with impaired EF and 0.81 (95% confidence interval: 0.63 to 1.04) in preserved EF ( $p = 0.720$  for subgroup interaction). Effects on all secondary end points were similar between groups (HR for all-cause mortality 0.84 and 0.91, respectively), and no  $p$  value for interaction was  $<0.48$ . CONCLUSIONS: The effect of beta-blockade with nebivolol in elderly patients with HF in this study was similar in those with preserved and impaired EF.